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Electron microscopy of SARS-CoV-2: a challenging task

Authors' reply

We thank Cynthia Goldsmith and colleagues for their interest in our recent Correspondence.¹ We described autopsy findings from patients who had died from COVID-19 and showed a systemic endotheliitis with evidence of loss of integrity of the endothelial monolayer.¹

The framework of endotheliitis provides an explanation for the unique predilection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in those individuals with hypertension, diabetes, or established cardiovascular disease, a group known to have pre-existing endothelial dysfunction. COVID-19-endotheliitis could also explain impaired microcirculatory function across different organs and the frequently observed prothrombotic state with in-situ clot formation. Endothelial infection and injury by SARS-CoV-1 has been shown.² Our demonstration of viral particles using electron microscopy (EM) is supported by several reports independently describing ultrastructural round virus-like particles in the setting of a SARS-CoV-2 infection.^{3–6} We demonstrated tubulo-reticular structures in the immediate vicinity of the spherical particles that are strikingly identical to SARS-CoV-1-associated membrane changes described by Goldsmith and colleagues in 2004.⁷ In our EM thin-section images, the virus-like particles were relatively large (mean diameter 180 nm [SD 10]). However, subsequent analysis of more EM images has revealed a mean particle size of 67 nm (SD 15 nm, median 65 nm, 95% CI 41–102; n=33). Zhu and colleagues⁵ noted that SARS-CoV-2 virions ranged from “about 60 to 140 nm”. In another recent study,⁶ virus-like particles in patients with confirmed SARS-CoV-2 infection were 70–110 nm in diameter. By comparison, SARS-CoV-1 viral particles analysed

with the same technique (ultrathin EM imaging) were 50–80 nm in diameter.^{7–10}

Goldsmith and colleagues have studied coronavirus isolates grown in cell culture, whereas our EM data of virus-like particles were obtained from a post-mortem kidney allograft obtained during autopsy. Since most other recent reports of patients with COVID-19 also describe postmortem findings, it remains unclear to what extent tissue type (cell culture, fresh biopsy material, or autopsy material), time to fixation, and postmortem autolysis alter subcellular structures in preparation for EM. This notwithstanding, these observed particles in patients with COVID-19 should be best designated as virus-like particles because definitive assignment of these structures as SARS-CoV-2 virions requires immuno-EM.

Investigations with vascular organoids that preceded our observations¹ showed that SARS-CoV-2 can infect human blood vessels via the ACE2 pathways, providing the first and direct evidence that the virus can indeed invade human vasculature.¹¹ Our findings have also been confirmed in descriptions of renal tropism of SARS-CoV-2, with detection of SARS-CoV-2 protein in human glomerular endothelial and epithelial cells.¹²

Importantly, our demonstration of virus cell infection in the kidney and endotheliitis¹ points to a general host inflammatory response causing hyperinflammation as a principal participant in the vascular pathology of COVID-19. Endothelial cell dysfunction, which might subsequently induce a prothrombotic state, could thus explain the vascular microcirculatory complications seen in different organs in patients with COVID-19.

We declare no competing interests.

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- 1 Varga Z, Flammer AJ, Steiger P. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; **395**: 1417–18.
- 2 Ye J, Zhang B, Xu J, et al. Molecular pathology in the lungs of severe acute respiratory syndrome patients. *Am J Pathol* 2007; **170**: 538–45.
- 3 Su H, Yang M, Wan C, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int* 2020; published online April 9. DOI:10.1016/j.kint.2020.04.003.
- 4 Kissling S, Rotman S, Gerber C, et al. Collapsing glomerulopathy in a COVID-19 patient. *Kidney Int* 2020; published online April 15. DOI:10.1016/j.kint.2020.04.006.
- 5 Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020; **382**: 727–33.
- 6 Menter T, Haslbauer JD, Nienhold R, et al. Post-mortem examination of COVID19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings of lungs and other organs suggesting vascular dysfunction. *Histopathology* 2020; published online May 4. DOI:10.1111/his.14134.
- 7 Goldsmith CS, Tatti KM, Ksiazek TG, et al. Ultrastructural characterization of SARS coronavirus. *Emerg Infect Diseases* 2004; **10**: 320–26.
- 8 Goldsmith CS, Miller SE. Modern uses of electron microscopy for detection of viruses. *Clin Microbiol Rev* 2009; **22**: 552–63.
- 9 Hsieh WJ, Hsiao CH, Paddock CD, et al. Immunohistochemical, in situ hybridization, and ultrastructural localization of SARS-associated coronavirus in lung of a fatal case of severe acute respiratory syndrome in Taiwan. *Hum Pathol* 2005; **36**: 303–09.
- 10 Qinfen Z, Jinming C, Xiaojun H, et al. The life cycle of SARS coronavirus in Vero E6 cells. *J Med Virol* 2004; **73**: 332–37.
- 11 Monteil V, Kwon H, Prado P, et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. *Cell* 2020; published online April 17. DOI:10.1016/j.cell.2020.04.004.
- 12 Puelles VG, Lutgehetmann M, Lindenmeyer MT, et al. Multiorgan and renal tropism of SARS-CoV-2. *N Engl J Med* 2020; published online May 13. DOI:10.1056/NEJMc2011400.



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